UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,382	03/14/2007	Kenneth Powell	NV2-020US	8889

93011 7590 12/24/2009

McCarter & English, LLP
Novartis Institutes for BioMedical Research, Inc.
265 Franklin Street
Boston, MA 02110

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,382	POWELL ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *5,6,9,10,16,21,22 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,19,23,24,26 and 29-38* is/are rejected.

7)☒ Claim(s) *11-15,17,18,20,27 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application, filed on 3/14/2007, is a national stage entry of PCT/GB05/01029, filed on 3/18/2005.

Priority

This application claims foreign priority to Application No. 0406279.0, filed on 3/19/2004.

Response to Restriction Requirement

1. Applicant's election with traverse of the species of 1-isopropenyl-3-(1-propyl-1H-benzoimidazol-2-ylmethyl)-1,3-dihydro-imidazo[4,5-c]pyridine-2-one for component (a), and 1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-phenyoxy-phenyl)-urea in the reply filed on 10/1/2009 is acknowledged. The traversal is on the ground(s) that the species do present a novel contribution over the prior art because the prior art does not teach the combination of (a) and (b). This is not found persuasive because, as discussed in the office action dated 4/28/2009, each of the individual species of components (a) and (b) are known in the prior art. The restriction was not based upon a known combination of (a) and (b) in the prior art, but rather than (a) and (b) are each known individually in the prior art. For example, the US 4,820,834 patent discloses benzodiazepine compounds of general formula (V), component (b), while the WO 98/45275 publication discloses compounds of general formula (I), component (a).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 5-6, 9-10, 16, 21-22, and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/1/2009.

3. The elected species for (a) and (b), 1-isopropenyl-3-(1-propyl-1H-benzoimidazol-2-ylmethyl)-1,3-dihydro-imidazo[4,5-c]pyridine-2-one and 1-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-phenyoxy-phenyl)-urea, have been found to be free of the prior art. Therefore, the search was expanded to other species of components (a) and (b).

4. Claims 1-4, 7-8, 11-15, 17-20, 23-24, 26-38 were examined.

5. Claims 1-4, 7-8, 19, 23-24, 26, and 29-38 are rejected.

6. Claims 11-15, 17, 18, 20, and 27-28 are objected to.

Claim Rejections-35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

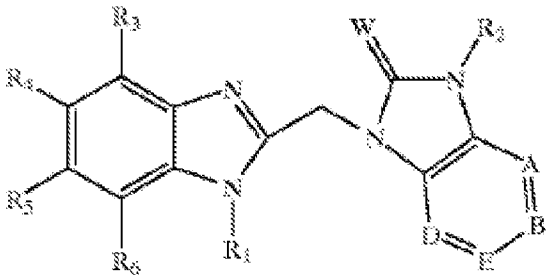
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

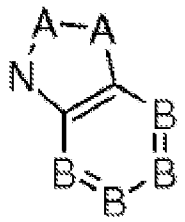
10. Claims 1-4, 7-8, 19, 23, 24, 26, 29-31, and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et. al., US Patent No. 6,489,338, in view of Tidwell et. al., US Patent No. 4,324,794, and further in view of Carter et. al., WO 2004/026843.

The claims are drawn to a pharmaceutical composition comprised of (a) an inhibitor of the RSV fusion protein, such a compounds of formula (I), and (b) a benzodiazepine derivative capable of inhibiting RSV replication, such as compounds of formula (V). The claims are also drawn to a composition in which the component (a) and (b) are each present in an amount from 0.025 weight % to 10 weight %.

Yu et. al. teaches that compounds of the formula shown below are effective for treating respiratory syncytial virus infection (Abstract; column 3, line 44-column 5, line 65). The compounds of the formula I taught by Yu et. al. are shown below:



Where R_3, R_4, R_5, R_6=H, etc.; R_2=H, C_{1-12} alkyl, C_{2-12} alkenyl, etc.; W=O; A, B, C, D = C-H, or N, etc.; R_1=-(CR'R")$_n$-X; n=0; X=H (R_1=H) (column 3, line 44-column 4, line 48). These compounds correspond to the claimed compounds of component (a), where R_1, R_2, R_3=H; X=bond when Y=H; Z=CR_6R_7; R_6=H; R_7=H; Q=



A=C or N; A is optionally substituted with O via a double bond; B=C or N.

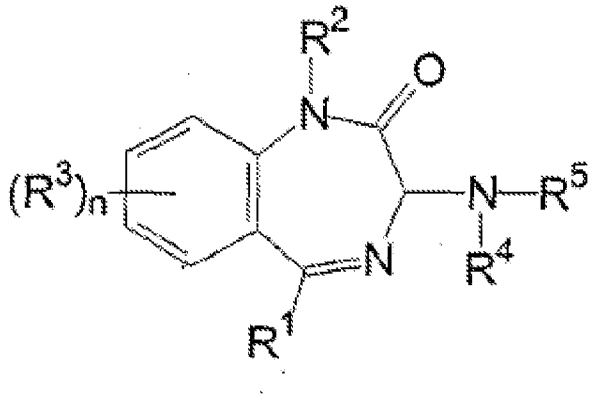
Yu et. al. teaches that the compounds of formula I inhibit the respiratory syncytial virus (column 1, lines 8-38; column 3, lines 10-20). Therefore, as it is taught that the compounds treat and inhibit the respiratory syncytial virus, it would have been prima facie obvious that the fusion protein produced by the virus would have been inhibited. Yu et. al. teaches the compounds in a pharmaceutical composition with acceptable carriers, and various routes of administration (column 137, line 38-column 138, line 9).

Yu et. al. does not explicitly teach that compounds such as bis(5-amidino-2-benzothiazolyl)-methane are present in compositions to inhibit the respiratory syncytial

virus, or a method of treating the respiratory syncytial virus with a composition comprised of the compound.

Tidwell et. al. teaches that bis(5-amidino-2-benzothiazolyl)-methane is effective at treating and inhibiting the respiratory syncytial virus (Abstract; column 2, lines 25-27). Tidwell teaches treatment of the respiratory syncytial virus in humans, via different routes of administration, and as such teaches the presence of the compound in a pharmaceutical composition with acceptable carriers (Abstract; column 2, lines 35-60). While Yu et. al. and Tidwell et. al. do not explicitly teach that the compounds are present in a pharmaceutical composition at a weight percent range from 0.025 to 10 %, different dosages are taught by both (Tidwell et. al., column 2, lines 35-4, and column 12, claim 2; Yu et. al., column 138, lines 10-24). The development of optimum weight % ranges of various compounds in pharmaceutical compositions to increase stability, and effectiveness is well known in the art; therefore, it would have been obvious to formulate a pharmaceutical composition comprised of the compounds taught by Yu et. al. and Tidwell within the weight % range from 0.025 to 10.

Yu et. al. and Tidwell et. al. do not teach that the pharmaceutical compositions also comprise a benzodiazepine derivative such as compounds of formula (V). Carter et. al. teaches that pharmaceutical compositions comprised of benzodiazepine compounds which are effective in treating and inhibiting respiratory syncytial virus (p. 1, lines 4-5 and 21-25; p. 35, lines 5-9). The benzodiazepine compounds taught by Carter et. al. which correspond to the claimed benzodiazepine compounds are shown below:



Where R^1=C_{1-6} alkyl, aryl (preferably phenyl); R^2=H, etc.; R^3=halogen, hydroxyl, C_{1-6} alkyl, etc.; n=0 to 3; R^4=H, etc.; R^5=-X-R_6; X=C(O); R_6=aryl, heteroaryl, etc. (p. 1, line 21-p. 2, line 22; p. 3, lines 18-20). Additionally, Carter et. al. teaches that heteroaryl groups for R^6 include pyridyl, pyrazinyl, furanyl, thienyl, and other heteroaryl groups (p. 7, lines 16-29). Carter et. al. teaches the benzodiazepine compounds in a pharmaceutical composition with acceptable carriers (p. 37, lines 19-32), and that the composition can contain up to 85 % by weight of the claimed anti-viral compounds (p. 37, lines 22-26). It is also taught that the benzodiazepines can be combined with other anti-viral compounds for simultaneous, separate, or sequential administration (p. 36, lines 22-28). Administration of the compositions to human patients is taught (p. 35, lines 10-14).

One of ordinary skill in the art, at the time of the invention, would have been motivated to prepare a pharmaceutical composition comprised of the compounds taught by Yu et. al., Tidwell et. al., and Carter et. al., because it is taught that all of these compounds are effective for treating respiratory syncytial virus. It is obvious to combine two or more agents in a composition that are taught by the prior art to be used for the

same purpose, absent unexpected results. As the compounds are taught to be effective for treating individuals afflicted with respiratory syncytial virus and in inhibiting the virus, one of ordinary skill in the art would have expected success in combining the compounds in a composition, and in treating the viral infection with the composition. Additionally, Carter et. al. teaches that the benzodiazepine compounds can be combined with other anti-viral agents, and that the agents can be administered together, sequentially, or separately. As the compounds taught by Yu et. al. and Tidwell et. al. are anti-viral compounds, it would have been obvious that the compounds could be combined with the diazepine compounds taught by Carter et. al. and administered together, sequentially, or separately.

Claim Rejections-Obviousness Type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-4, 7-8, 23, 24, 26, 29-31, and 34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 12, 16, 17, 18, 19, 23, 24, 26, 29-31, and 34 of copending Application No. 10593666. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions comprised of (a) an inhibitor of the RSV fusion protein and (b) a benzodiazepine compound capable of inhibiting RSV replication. Both sets of claims are also drawn to compositions in which (a) and (b) are present in the composition at a weight percent range between 0.025-10 %.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections-35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 32-33, and 35-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of an RSV infection, does not reasonably provide enablement for prevention of an RSV infection. Prevention is an absolute term, and implies that an event can be kept from occurring, under all

circumstances. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See M.P.E.P. 2164.08. The reference of Broughton et. al., *Expert Opin. Pharmacother.*, **4(10)**, pp. 1801-1808, (2003), is used in this rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the use of an inhibitor of the RSV fusion protein and (b) a benzodiazepine compound in the manufacture of a medicament for use in treating or preventing an RSV infection, and a product comprised of components (a) and (b) for treating or preventing an RSV infection. Thus, the claims taken together with the specification imply that an RSV infection, in addition to be treated, can always be prevented. Thus, the claims are drawn to treatment and prevention of an RSV infection, under all conditions. Due to the inclusion of preventing an RSV infection, the claims are considerably broad.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The prior art provides evidence that while the incidence of developing more severe symptoms of respiratory syncytial virus can be reduced by pharmaceutical therapies, prevention of the virus as a whole has not yet been accomplished. Broughton et. al. teaches that respiratory syncytial virus currently poses an enormous burden on the health care system, due to hospitalizations and mortalities resulting from infection (Abstract; p. 1801, lower paragraph-p. 1802, left column, top paragraph). Broughton et. al. teaches that prevention of respiratory syncytial virus is most successful when immunoprophylaxis is employed, but unfortunately, there is presently no safe or effective vaccine (p. 1804, left column, last paragraph, first two sentences). It is taught the even when immunotherapy is used as a prophylactic measure, while there is a reduction in the amount of hospitalization time, infection with the respiratory syncytial virus is not prevented in a number of cases (p. 1804, right

column, first full paragraph). Additionally, it is taught that significant side effects are observed with some prophylactic treatments (p. 1804, right column, first full paragraph). Broughton et. al. teaches that handwashing also is an effective measure in controlling the nosocomial transmission of the virus (p. 1805, left column, lower paragraph-right column, top paragraph). It is also taught that as yet, no study has demonstrated that prophylaxis, regardless of the different therapy used, has proven to be cost-effective in terms of reducing costs associated with hospitalizations (p. 1804, right column, last sentence-p. 1805, left column, top paragraph). As such, the prior art provides evidence that developing effective prophylaxis for respiratory syncytial virus infections is still experimental, and that considerably uncertainty exists regarding the success of preventive measures.

(5) The relative skill of those in the art:

The relative skill of one in the art is expected to be high, such as that of an MD or PhD in immunology.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for treating respiratory syncytial virus with a composition comprised of (a) an inhibitor of the RSV fusion protein and (b) a benzodiazepine compound capable of inhibiting RSV infection.

However, the specification does not provide guidance for prevention of respiratory syncytial virus in the population at large.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the evidence provided by the prior art and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections-35 USC § 101

15. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-33, and 37-38 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a use of a (a) an inhibitor of the RSV fusion protein and (b) a benzodiazepine compound, in the manufacture of a medicament for use in treating or preventing an RSV infection. Claims that are drawn to a 'use' of a product or composition without a series of steps, method, or a specific utility, are not patentable subject matter. Particularly, it is not cited in the claims as to how the compounds (a) and (b) will be 'used' in the manufacture of a medicament. As such, it is uncertain whether the claims are drawn to a method of making a medicament, or whether the claims are drawn to a product, such as the medicament itself.

Claim Rejections-35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 32-33, and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a use of a (a) an inhibitor of the RSV fusion protein and (b) a benzodiazepine compound, in the manufacture of a medicament for use in treating or preventing an RSV infection. Particularly, it is not cited in the claims as to how the compounds (a) and (b) will be 'used' in the manufacture of a medicament. As such, it is uncertain whether the claims are drawn to a method of making a medicament, or whether the claims are drawn to a product, such as the medicament itself. Therefore, the claim limitations can not be determined, due to the indefinite language.

18. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 35 recites the limitation "preventing an RSV infection" with a product according to claim 34. However, claim 34 is drawn to a product comprising components (a) and (b) for separate, sequential, or simultaneous use in the treatment of the animal or human. However, claim 34 does not contain language drawn to "prevention". While for product claims, language drawn to a method or use are not considered pertinent to

the patentability of the claims, the claims are still considered in their entirety. There is insufficient antecedent basis for this limitation in the claim.

Claim Objections

20. Claims 11-15, 17, 18, 20, 27, and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-every other Friday 8:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627